REVIEW ARTICLE

New discoveries in the pathophysiology, genetics, and treatment of IgA nephropathy

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ABSTRACT

IgA nephropathy has made significant improvement in recent years. The successful identification of several genetic susceptibility loci, the development of the multi pathogenesis model, the adoption of the Oxford pathology scoring system, and the formalisation of the Kidney Disease Improving Global Outcomes (KDIGO) consensus treatment recommendations are some of the significant new directions and most recent developments we highlight in this article. We concentrate on the most recent genetic discoveries that support the significant role of hereditary variables and provide an explanation for some of the geoethnic differences in illness risk. The majority of IgA nephropathy susceptibility loci identified so far encode proteins involved in the upkeep of the intestinal epithelial barrier and the immune system's reaction to mucosal infections. The coordinated pattern of interpopulation allelic differentiation across all genetic loci interacts with variance in local pathogens and the incidence of the disease, pointing to a possible role for multilocus adaptation in shaping the current landscape of IgA nephropathy. Importantly, one of the new targets for potential therapeutic intervention, the "Intestinal Immune Network for IgA Production," appeared. We interpret these results in light of the multihit pathogenesis hypothesis and our current understanding of IgA immunobiology. Finally, we offer our viewpoint on the available therapeutic choices, talk about clinically ambiguous areas, and highlight ongoing clinical trials and translational investigations.

Key Words: *Adaptive immunity complement system; GWAS*

INTRODUCTION

IgA nephropathy (IgAN) has been acknowledged as the most prevalent kind of primary glomerulonephritis and a significant contributor to chronic kidney disease and end-stage kidney failure since it was first described in 19681. IgAN research has advanced significantly in recent years, partly as a result of increasing collaborative efforts that made it possible to carry out robust clinical and genetic studies [1]. New genetic susceptibility loci have been found, the multihit pathogenesis model has been developed based on research on IgA1 O-glycosylation and anti-glycan antibodies, the Oxford pathology rating system has been implemented, and IgAN therapy recommendations have been formalised. We give an update on these advances, offer our viewpoint on the treatment recommendations, list the remaining areas of uncertainty, and highlight significant new directions in this assessment.

Children, the elderly, and young people are the most often affected groups by IgAN. A wide range of clinical signs are present in the condition, from asymptomatic microscopic hematuria to a more severe course marked by persistent proteinuria and a sharp decline in renal function. Kidney biopsy is necessary for the accurate diagnosis of IgAN, which is characterised immunohistologically by dominant or codominant glomerular IgA deposits. The glomeruli should be diffusely involved, and the IgA should be at least 1+ in intensity and, in most cases, 2+ or higher. IgA typically exhibits a clear dominating staining, while IgG and/or IgM staining is typically weaker and more varied. Most of the deposits are made up of polymeric IgA of the IgA1 subtype [2]. A total of 100% of the 2249 cases of IgAN gathered from 13 published biopsy series tested positive for IgA, 43% for IgG, and 54% for IgM. The majority of the time, the greater staining for

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light chain relative to light chain reflects the prevalence of IgA1 in the circulation. IgAN has a wide range of histologic characteristics that are common to most immune complex-mediated proliferative glomerulonephritis [3]. These include injuries with no or very few light microscopically detectable abnormalities, mesangial hypercellularity, focal or diffuse endocapillary proliferative, necrotizing and crescentic lesions, and, less frequently, membranoproliferative patterns of injury. Red blood cell casts and acute tubular damage may coexist. With accompanying tubular atrophy and interstitial fibrosis, focal or diffuse segmental and global glomerulosclerosis progresses during the chronic stages. According to electron microscopy, the mesangium is the primary location of the glomerular deposits in IgAN, with variable subendothelial and uncommon subepithelial deposits in the more severe cases. Paramesangial refers to the region where mesangial deposits commonly collect beneath the glomerular foundation membrane reflecting over the mesangium. Hematuria can result from the glomerular basement membranes showing localised weakening, rupture, or remodeling [4]. A systemic type of IgA vasculitis with renal symptoms, Henoch-Schönlein purpura nephritis primarily affects children under the age of 18. A tetrad of visible purpura, arthralgia, stomach pain, and renal dysfunction commonly characterise this illness's symptoms. Although Henoch-Schönlein purpura nephritis is typically self-limited in children, chronic or progressive renal impairment and persistent proteinuria are frequently seen in adult instances [5]. According to electron microscopy, the mesangium is the primary location of the glomerular deposits in IgAN, with variable subendothelial and uncommon subepithelial deposits in the more severe cases. Paramesangial refers to the region where mesangial deposits commonly collect beneath the glomerular foundation membrane reflecting over the mesangium. Hematuria can result from the glomerular basement membranes showing localised weakening, rupture, or remodelling. A systemic type of IgA vasculitis with renal symptoms, Henoch-Schönlein purpura nephritis primarily affects children under the age of 18. A tetrad of visible purpura, arthralgia, stomach pain, and renal dysfunction commonly characterise this illness's symptoms. Although Henoch-Schönlein purpura nephritis is typically self-limited in children, chronic or progressive renal impairment and persistent proteinuria are frequently seen in adult instances. Similar to IgA nephropathy in terms of histologic spectrum, renal disease also exhibits crescents and glomerular necrosis, but more frequently. In contrast to IgAN, Henoch-Schönlein purpura nephritis exhibits a higher frequency of glomerular fibrin staining, but otherwise has a comparable immunofluorescence profile. Prior to the World Health Organization's classification of lupus nephritis, heuristic classification schemes for IgAN were based on the pattern and severity of the proliferative and sclerosing lesions. As the first evidence-based schema, the Oxford IgAN classification was developed by a working group of more than 40 nephrologists and pathologists from the International IgA Nephropathy Network and the Renal Pathology Society [6,7]. It was designed to find repeatable histologic characteristics that can predict disease development in a sizable illness cohort with established outcomes; as a result, it is a scoring system rather than an exhaustive categorization. 265 IgAN cases, 78% of which were adults, were included in the discovery cohort from Europe, North America, and Asia. Patients with very mild disease,

rapidly progressing glomerulonephritis, and advanced chronic disease were underrepresented in the study because cases with proteinuria of less than 0.5 g per day, initial Estimated Glomerular Filtration Rate (eGFR) of less than 30 ml/min per 1.73 m², and progression to End-Stage Renal Disease (ESRD) within 12 months of biopsy were excluded. Segmental glomerulosclerosis (S), diffuse mesangial hypercellularity (M), and tubular atrophy/interstitial fibrosis involving > 25% of the cortical area were three reproducible histologic features that independently correlated with both the rate of renal functional decline and renal survival end points (defined as 50% reduction in eGFR or ESRD) (T). Even worse results were linked to tubular atrophy/interstitial fibrosis involving > 50% (vs. 26–50%) of the cortex. Response to immunosuppressive medication was linked to Endocapillary hypercellularity (E). The MEST score (M, Mesangial Hypercellularity; E, Endocapillary Hypercellularity; S, Segmental Glomerulosclerosis/Adhesion; T, Tubular Atrophy/Interstitial Fibrosis) assigns the designations M0 or M1 for Mesangial Hypercellularity Involving 50% or>50% of Glomeruli, respectively; E0 or E1 for Endocapillary Hypercellularity Involving 0. A minimum of one glomerulus, as well as the stages T0, T1, and T2 for tubular atrophy/interstitial fibrosis affecting, respectively, 25%, 26%–50%, and more than 50% of the cortical area. The study design restricted the Oxford system's capacity to completely address the influence of crescents and particular immunofluorescence features, such as the existence of peripheral capillary wall deposits of IgA and codeposits of IgG. This is the system's main weakness [8]. Numerous research, particularly those involving paediatric patients, have tried to evaluate the MEST lesions' prognostic ability in separate cohorts from North America, Europe, and Asia. With occasional exceptions, these studies have typically supported the predictive significance of different components using univariate and multivariate analysis. The largest meta-analysis, which had 3893 IgAN cases and was based on 16 retrospective cohort studies, confirmed the predictive effect of the M, S, and T lesions but did not confirm the prognostic value of the E score. The T score was consistently the most significant predictor of poor renal outcomes across all cohorts, despite the E score showing some of the weakest and most variable relationships with disease progression. A meta-analysis of these studies revealed that the C score, which is defined as the presence of any crescents, was strongly associated with the progression to kidney failure. In addition, 5 of 16 studies—4 Asian and 1 European—with a total of 1487 patients examined the association of crescents with clinical outcomes [9]. Last but not least, the recently released VALIGA (European Validation of the Oxford Classification of IgAN) study of 1147 patients from 13 different European countries provided an independent validation of the predictive value of the M, S, and T lesions across a wider spectrum of the disease (not included in the above meta-analysis). Once more, results were not related to the E score. Nevertheless, the association between some factors, such the E score, and clinical outcomes as all of the published validation studies have been based on retrospective observational data, may have been influenced by exposure to immunosuppressive treatment [10].

CONCLUSION

In conclusion, the Oxford scoring system is a significant step toward better prognostication and standardised diagnosis, although it may still need to be worked upon in order to be more useful for prognostication. A sizable randomised controlled trial where therapy decisions are not based on pathology is necessary for a more thorough evaluation of the scoring system. The TESTING project might offer a special chance to validate and improve this scoring method while eliminating any inherent treatment biases. IgAN must be diagnosed through kidney biopsy, hence it is still challenging to determine the true illness prevalence. Mesangial IgA deposits are surprisingly common; prevalence estimates from necropsy investigations range from 4% to 16%, depending on the population examined. Similar to this, IgA deposition has been found to occur up to 16% of the time in protocol biopsies of living or cadaveric kidney donors in Japan. According to these findings, subclinical IgA deposition is widespread and may be particularly common in East Asian populations. A relative frequency of IgAN among all instances of primary glomerulonephritis in a biopsy registry is another frequently mentioned indicator of IgAN prevalence.

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